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Abstract: Electroencephalography (EEG) examines the functional state of the brain. High-frequency oscillations (HFOs) in the ripple (80-200/250 Hz) and fast ripple (200/250-500/600 Hz) bands have recently been attracting attention, and their recording has been enabled by advancements in digital EEG techniques. The detection of HFOs was previously limited to intracranial EEG, but fast oscillations (FOs) in the gamma (40-80 Hz) and ripple bands can now be detected over the scalp. HFOs and FOs have been shown to be related to epileptogenicity in intracranial EEG and scalp EEG, respectively. A large number of FOs are found in the scalp EEGs of pediatric patients with various epileptic encephalopathies, particularly West syndrome. FOs are suggested to be a biomarker of the epileptogenic cortical region in epilepsy surgery. FOs are detectable even in patients with idiopathic focal epilepsies, including benign epilepsy with centrotemporal spikes and Panayiotopoulos syndrome, who are not generally candidates for operation. The detection of HFOs and FOs may provide clues to the pathophysiology of epilepsy and the relationship between HFOs and cognitive dysfunction.

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Review

Epileptic High-frequency Oscillations in Scalp Electroencephalography

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Electroencephalography (EEG) examines the functional state of the brain. High-frequency oscillations (HFOs) in the ripple (80-200/250 Hz) and fast ripple (200/250-500/600 Hz) bands have recently been attracting attention, and their recording has been enabled by advancements in digital EEG techniques. The detection of HFOs was previously limited to intracranial EEG, but fast oscillations (FOs) in the gamma (40-80 Hz) and ripple bands can now be detected over the scalp. HFOs and FOs have been shown to be related to epileptogenicity in intracranial EEG and scalp EEG, respectively. A large number of FOs are found in the scalp EEGs of pediatric patients with various epileptic encephalopathies, particularly West syndrome. FOs are suggested to be a biomarker of the epileptogenic cortical region in epilepsy surgery. FOs are detectable even in patients with idiopathic focal epilepsies, including benign epilepsy with centrotemporal spikes and Panayiotopoulos syndrome, who are not generally candidates for operation. The detection of HFOs and FOs may provide clues to the pathophysiology of epilepsy and the relationship between HFOs and cognitive dysfunction.

Key words: electroencephalogram, high-frequency oscillations, fast oscillations, time-frequency analysis, epilepsy

Electroencephalography (EEG) records the weak electrical activity emanating from the central nervous system. EEG data reflect the sum of the post-synaptic potentials of cerebral cortical neurons. EEG is the main tool used to evaluate the functional state of the brain, and it provides a great deal of information regarding brain functions.

In traditional clinical EEG, the observed activity extends to the beta band (14-40 Hz). The EEG signal range is now greatly widened to include the gamma (40-80 Hz), ripple (80-200/250 Hz), and fast ripple (200/250-500/600 Hz) bands due to advancements in digital EEG techniques. High-frequency activities — especially high-frequency oscillations (HFOs) including ripple and fast ripple oscillations in EEG — are related to epileptogenicity [1-3]. The relationship of HFOs to epileptogenicity is considered to be stronger than the relationship of spikes to epileptogenicity.

Regarding the generative mechanisms of HFOs, the contribution of population spikes, *i.e.*, bursts of action potentials, was demonstrated in animal models and simulation studies *in silico* [4-8]. In the initial stage of studies on high-frequency activities, HFOs were recorded from microelectrodes inserted into the hippocampi and other epileptogenic regions [9,10]. Next, the detection of HFOs using clinical intracranial electrodes was reported, and rapidly enhanced the clinical significance of HFOs [11]. We reported the detection of ripples in scalp-recorded EEG [12]. Ripple and gamma oscillations over the scalp are collectively termed "fast oscillations (FOs)."

Herein we review the detection method, meaning, clinical significance, and future outlook of high-fre-

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quency activity in scalp EEG, based on recent reports.

Fast Oscillations in Scalp EEG

The advantages of the scalp recording of HFOs over intracranial recording include scalp recording's noninvasiveness and ease of application. These advantages make it possible to analyze HFOs, particularly ripple oscillations, in the EEG of patients with idiopathic epilepsies who are not generally candidates for operation. Another advantage of scalp recording is that scalp EEG can cover a much wider area of the cortex than intracranial EEG. One disadvantage of scalp recording is that the signal from the cortical surface decays markedly in scalp EEG because of the presence of poorly conductive tissue such as the dura mater, skull, and scalp, between the cortex and electrodes. This decay makes it difficult to detect low-amplitude cortical signals over the scalp. In addition, artifacts and electromyograms are likely to contaminate scalp EEG, and they should be carefully excluded from analyses.

It is unknown whether the HFOs in scalp EEG mirror those in intracranial EEG. Regarding the relationship between these two types of HFOs, simultaneous scalp and intracranial EEG recording demonstrated that scalp HFOs reflect cortical HFOs [13]. HFOs in scalp and intracranial EEG may not have the same meaning, however. The size of the electrodes and the distance from the cortical surface to the electrodes differ between scalp and intracranial EEG, and thus the cortical area covered by one electrode also differs. There is also the problem of the attenuation of cortically generated signals in scalp EEG, as mentioned above. Signals in scalp EEG are likely to have lower frequencies than those in intracranial EEG, and only high-amplitude cortical signals are detectable over the scalp.

It has been suggested that HFOs > 80 Hz are related to epileptogenicity in intracranial EEG. In scalp EEG, however, gamma activities are also considered to be related to epileptogenicity, and therefore gamma oscillations are included in FOs along with ripple oscillations. To date, reliable observations of the activity over the scalp are limited up to the ripple band, but it has been reported that fast ripples might be detectable even in scalp EEG [14].

Detection of Scalp FOs

Methods to detect FOs from EEG data include frequency filters and time-frequency analyses [15]. FOs are usually veiled by low-frequency waves and are therefore difficult to detect. FOs are rendered clearly detectable by reducing the low-frequency activity with the use of low-cut frequency filters. In time-frequency analyses, power spectra (arrays of the signal intensity at each individual frequency level) are computed by applying frequency analyses such as the short-time Fourier transform (Gabor transform) and the wavelet transform to a series of short sections of EEG data. Each point in a panel of time-frequency analysis is drawn on the basis of the thus obtained power spectra. An FO is indicated as a high-intensity blob in such a panel (Fig. 1).

To avoid the misidentification of FOs, their presence is often confirmed by combining a review of filtered EEG traces and a time-frequency analysis [16]. Artifacts and muscle activity generally have irregular morphology and are thus not associated with a clear blob in a time-frequency analysis. Therefore, the true FOs can be morphologically and spectrally differentiated from artifacts and muscle activity. This procedure is time-consuming and may be affected by the subjective decisions of investigators. The development of software for the automatic detection of FOs is needed in order to solve such problems [17].

Scalp FOs in West Syndrome

Scalp FOs are detectable in childhood epilepsy, particularly West syndrome. There are a large number of FOs in the ictal EEGs of children with epileptic spasms and interictal hypsarrhythmia, which is a state involving a "storm" of FOs, in which the rate of FOs is estimated to be approx. 100 times higher than that in adult patients [18]. It has been suggested that these FOs might indicate the degree of epileptogenicity, because they decrease with the amelioration of hypsarrhythmia by adrenocorticotropic hormone therapy. Iwatani *et al.* reported that the ictal FOs of epileptic spasms on scalp EEG showed a strong association with neuroimaging lesions that were presumed to be in the epileptogenic zone in symptomatic West syndrome [19]. Nariai *et al.* reported that, prior to the ictal motor manifestation, focal ictal gamma and beta activity emerged in the ictal scalp EEGs of patients experiencing epileptic spasms,

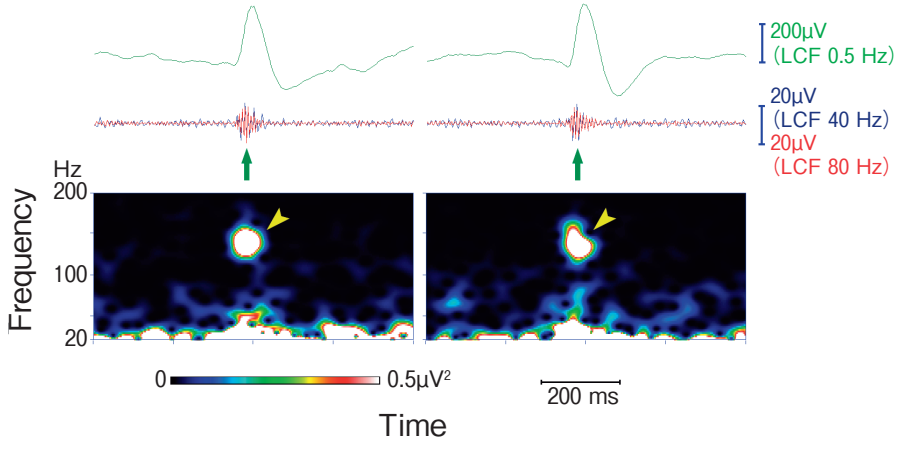

Fig. 1 Ripple oscillations in the scalp EEG recorded from a child with benign epilepsy with centrotemporal spikes. Representative spikes (*arrows*) are associated with ripple oscillations (EEG traces filtered at 0.5, 40, and 80 Hz shown in green, blue, and red, respectively). EEG data are presented in a referential montage, using the average of A1 and A2 (Aav) as the reference. Note that spike-related ripples with at least four consecutive oscillations are clearly observed. The time-frequency spectra exhibit spectral blobs with peak frequencies at around 140 Hz (*arrowhead*) in temporal association with the corresponding spikes.

and the asymmetric peak amplitude of ictal gamma activity in the centroparietal areas was correlated with asymmetric semiology [20]. They also reported that most of the visually symmetric spasms showed asymmetry in peak amplitudes and interhemispheric onset timing differences in both ictal gamma and beta activity.

As described above, FOs may be a biomarker for epileptogenicity, but their interpretation must be done carefully. For example, the signal amplitude is decreased in cases of severe brain atrophy because the distance between the cortical surface and the electrodes is relatively large in scalp EEG. When the epileptogenic hemisphere is markedly atrophic, FOs may appear dominant over the contralateral unaffected hemisphere, and in such cases the meaning of FOs must be understood in combination with other findings, including brain imaging [21].

FOs are observed not only in West syndrome but also in association with the burst part of the suppression-burst pattern in epileptic encephalopathy during early infancy, such as Ohtahara syndrome and early myoclonic encephalopathy [22].

Scalp FOs in Adult Epilepsy

FOs are detectable in scalp EEGs recorded not only in children but also in adults. It was reported that gamma and ripple oscillations were observed in scalp EEGs of adult patients with focal epilepsy, and the oscillations provided lower sensitivity but higher specificity than spikes in the identification of the seizure onset zone [23,24].

According to a report comparing bilaterally synchronous EEG discharges in adult focal and generalized epilepsy patients, the hemisphere of clinical lateralization and the ripple-dominant hemisphere were completely concordant in the focal epilepsy group. In contrast, in the generalized epilepsy group, the ripple detection rate was low, and all patients had anterior dominance without asymmetry [25].

FOs in scalp EEGs are thus indicated to be related to epileptogenicity in both adult and pediatric epilepsy patients.

Idiopathic Epilepsy in Childhood and Scalp FOs

As mentioned above, the advantages of analyzing FOs in scalp EEGs include the ease of recording and noninvasiveness, and childhood idiopathic epilepsies are thus appropriate candidates for investigation. Kobayashi *et al.* reported their serial analysis of spike-associated ripples in scalp EEGs of patients with benign epilepsy with centrotemporal spikes (BECTS) and patients with Panayiotopoulos syndrome (PS), which are representative idiopathic focal epilepsies in

childhood [26]. They detected ripples by extracting at most 30 spikes with the identical focus and averaging the spectra obtained through a time-frequency analysis. This procedure made it possible to eliminate noise and detect weak high-frequency activity. According to their results, after the last seizure, the EEG recordings tended to lose ripples first and to subsequently lose spikes during the follow-up periods. In addition, the peak-power values of the ripples also tended to decrease with the time elapsed from the last seizure. Thus, ripples were suggested to have a stronger relationship with epileptogenicity than spikes.

Qian *et al.* investigated the rates of interictal spikes and HFOs in pre- and post-methylprednisolone treatment scalp EEGs recorded from patients with atypical benign partial epilepsy (ABPE). They reported that the reduction of HFO rates by methylprednisolone treatment was greater than the reduction of spike rates [27].

We analyzed the relationship between spike foci and the rates of associated ripples in scalp EEGs recorded from patients with BECTS or PS in order to elucidate the pathophysiology of these epileptic syndromes [28]. In BECTS, the proportion of spikes with associated ripples was significantly higher in the spike-group with dipoles in the perirolandic areas (*i.e.*, a combination of the precentral and postcentral gyri) compared to the group with dipoles outside of the perirolandic areas. Areas with strong epileptogenicity were concordant with seizure symptomatology, and a close relationship was suggested between the origin of spikes and its epileptogenicity. In the PS group, the proportion of spikes with associated ripples was significantly higher in the spike-group with dipoles in the occipital lobes than in the patients with dipoles outside of the occipital lobes. Thus in PS, even when the spikes are multifocal, spikes originating from the occipital lobes might have a particular meaning.

Future Perspective

Prognostic prediction of seizures. BECTS and PS patients generally have good prognoses, and they do not always require treatment. There are, however, exceptional atypical cases that are intractable and involve associated cognitive dysfunction and behavior disorders, and patients with such epilepsy may need dedicated treatment. It is often difficult to provide a prognosis based on traditional clinical and/or EEG findings, such as rates of interictal spikes. van Klink *et al.* investigated ripples in children with rolandic spikes who were categorized into 3 groups: (1) patients with rolandic spikes but no epilepsy, (2) those with typical rolandic epilepsy, and (3) those with atypical and symptomatic rolandic epilepsy. Those authors reported that the number of visually detected ripples showed a significant positive correlation with the number of seizures [29]. The detection of FOs may have potential as a predictor of seizure prognosis, and this potential should be examined in future research.

Scalp FOs and cognitive function. In the spectrum of epileptic disorders with continuous spike-waves during slow wave sleep (CSWS) in EEGs, including ABPE, Landau-Kleffner syndrome, and epileptic encephalopathy with CSWS, much more intense FOs are found compared to BECTS and PS [12,27]. Intracranial physiological high-frequency activities are known to be involved in higher brain functions such as cognition and language [30,31]. The cognitive function of patients with CSWS is often impaired. Abnormal FOs might cause brain dysfunction by interfering with physiological high-frequency activities. Even among patients who show similar CSWS in EEG, the intellectual prognosis varies considerably. It is possible that the degree of the intensity of FOs influences cognition;this remains an issue for future study.

Conclusions

Advances in EEG analysis techniques have enabled the detection of FOs from scalp EEGs. It is hoped that new techniques will be useful for both the search of epileptogenic zones and the elucidation of the pathophysiology of epilepsy and the relationship between FOs and cognitive dysfunction. Continued progress in EEG analysis is expected.

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